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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,144	08/21/2001	Glenn R. Larsen	GFN-5213CP6CN	9733

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,144	LARSEN ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner: Xiaozhen Xie.

Applicant's amendment of the claims received on 21 November 2005 has been entered. Applicant's remarks received on 14 July 2006 are acknowledged.

As indicated in the interview summary on 24 August 2006, upon further review and consideration, the finality of the previous office action (29 August 2005) is withdrawn.

Claims 1-57 have been cancelled. Claims 58-71 are pending and under examination.

Claim Objections/Rejections Withdrawn

The rejection of claim 59, 61 and 67 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement (a new matter rejection), is withdrawn in response to Applicant's argument that the diseases of claims 59, 61 and 67 are described in the specification, and that the term "P-selectin ligand protein" encompasses fusion proteins.

New Grounds of Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to: a method of reducing inflammation in a subject having an inflammatory disease or having a condition characterized by selectin-mediated intercellular adhesion, comprising administering a composition comprising a fusion protein comprising the amino acids 42-60 of SEQ ID NO: 2 and a non-P selectin ligand amino acid sequence; and a method of reducing inflammation in a subject having myocardial infarction or a thrombotic disorder, comprising administering a composition comprising a soluble P-selectin ligand protein comprising the amino acids 42-88 of SEQ ID NO: 2.

The claims are broad in that they encompass reducing inflammation in a subject having a disparate listing of many diseases by administering a composition comprising a fusion protein comprising a P-selectin ligand protein fragment comprising the amino acids 42-60 of SEQ ID NO: 2, or by administering a composition comprising a P-selectin ligand protein fragment comprising the amino acids 42-88 of SEQ ID NO: 2. The specification teaches that during inflammation, leukocytes adhere to the vascular endothelium and enter subendothelial tissue, an interaction mediated by specific binding of selectins to ligands on target cells. The instant invention relates to polypeptides that

are capable of blocking the interaction of leukocytes with endothelial cells, and by doing do, to inhibit inflammation. Applicant discloses several P-selectin glycoprotein ligand-1 (PSGL-1) fragments and their Fc chimeric fusion proteins, such as 253.Fc (amino acids 42-294 of SEQ ID NO: 2), 148.Fc (amino acids 42-189), 47.Fc (amino acids 42-88), and 19.Fc (amino acids 42-60). Applicant discloses the results of these fragments in binding to P and E-selectins (Fig. 12). Applicant shows that 253.Fc, 148Fc and 47.Fc strongly bind to P-selection and they also bind to E-selectin with the same affinity. Applicant shows that although the binding of 19.Fc to the P-selectin is much weaker than other fragments, 19.Fc barely binds E-selectin (Fig. 23-24). Applicant further discloses the ability of some peptides in inhibiting P-selectin binding to its ligand in an in vitro assay (Example 13, and Fig. 30). Of those, two peptides: one having a sequence of amino acids 44-53 of SEQ ID NO: 2, the other one having a sequence of amino acids 42-56 of SEQ ID NO: 2 and a cystein residue at the C-terminus, show P-selectin/PSGL-1 binding inhibition. However, Applicant does not shown any fragment comprising the amino acids 42-60, or comprising the amino acids 42-88 of SEQ ID NO: 2 have specific inhibitory activity for P-selectin/PSGL-1 binding. Further, Applicant has not provided teachings to indicate that such P-selectin/PSGL-1 binding inhibition induced by the PSGL-1 fragment is sufficient to inhibit leukocyte/endothelial cell interaction, and is sufficient to reduce inflammation in any recited disease. Further, Ridger et al. (Am. J. Pathol., 2005, 166(3): 945-952) teach that leukocyte rolling during inflammation can continue in the absence of optimal P-selectin/PSGL-1 interaction because cells can use an alternative mechanism that involves P-selectin, L-selectin, and sLe^X-bearing ligands (abstract). Ridger et al.

teach that L-selectin and a sLeX-bearing ligand support significant leukocyte rolling although such interaction is only revealed after inhibition of high-affinity P-selectin/PSGL-1 interaction (pp. 951, left column, last paragraph). Therefore, the specification does not provides sufficient guidance to allow the artisan to reducing inflammation in subjects having all those diseases recited in the claims.

In addition, the claims recite the composition comprising a fusion protein comprising: (a) amino acids sequence comprising amino acids 42-60 of SEQ ID NO: 2, and (b) a non-P selectin ligand amino acid sequence. The specification describes that the second amino acid sequence is derived from a protein selected from the group consisting of an antibody, a cytokine, a growth factor, a differentiation factor, a hormone, an enzyme, a receptor or fragment thereof and a ligand (pp. 7, lines 13-15). Applicant has disclosed a fusion protein comprising an Fc portion of an immunoglobulin. Applicant has not provided teachings that a fusion protein comprising amino acids 42-60 of SEQ ID NO: 2 and any other sequence, derived from a cytokine, a growth factor, a differentiation factor, a hormone, an enzyme, etc., can be used as an anti-inflammatory agent. In particular, many cytokines are pro-inflammatory and they could exhibit opposite effects as the instant invention intends to have.

Applicant argues in the reply received on 7 January 2005 that the specification provides assays for measuring interaction between cells expressing P-selectin and those expressing PSGL-1, for example, between PSGL expressing-COS cells and P-selectin expressing-CHO cells, and that while the specification does not specifically use leukocytes and endothelial cells in such interaction assays, compounds identified as

blocking the interaction can be used for blocking interaction between any two cells. Applicant further argues that Ulbrich, cited in the 10 August 2004 office action as rendering the claimed invention non-enabling, is misleading and irrelevant, because Ulbrich reported no therapeutic effect for treatment of myocardial infarction using rPSGL-Ig. Applicant argues that the instant claims are drawn to reducing inflammation in a subject, and ineffectiveness in treating myocardial infarction has no bearing on the instant claims. Applicant submitted post-filing references (Wang, 2001; Gasser, 2002; Battistini, 2003) evidencing that a soluble form of PSGL protein including the first 47 amino acids from the N-terminus fused to human IgG1 was effective in reducing inflammation in various conditions.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The assay system, which uses the PSGL expressing-COS cells and the P-selectin expressing-CHO cells, is a completely different system from the reference of Theoret et al. (2001) provided by Applicant. The COS and CHO cell system can only detect binding between P-selectin and PSGL-1. It does not resemble the in vivo situation. Theoret set up an in vivo system involving flowing platelet activation and their binding to neutrophils after circulation over intact and damaged arterial surfaces. Theoret teaches that a soluble form of PSGL-1 (rPSGL-Ig) can inhibit the interaction between leukocytes/platelets and endothelial cells. Theoret does not confirm any PSGL-1 fragments other than rPSGL-Ig having the inhibitory activity for the interaction between leukocytes/platelets and endothelial cells.

Further, Ulbrich summarizes in the article published in 2003 drug candidates that failed in clinical trails to protect against inflammation induced by ischemic conditions including antibodies against all selectins, either individually or in combination, and rPSGL-1-Ig (pp. 644, left column, lines 2-7). Ulbrich reported no therapeutic effect of these drug candidates for reducing inflammation induced by, for example, myocardial infarction.

Applicant submitted post-filing references by Wang (2001), Gasser (2002), and Battistini (2003), evidencing that a soluble form of PSGL protein including the first 47 amino acids from the N-terminus fused to human IgG1 was effective in reducing inflammation in various conditions. However, MEPE 2164.05(a) states "Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing." There is no sufficient teaching, based on applicant's specification, that an artisan would identify the PSGL-1 fragments and use the molecules for reducing inflammation in all diseases or conditions recited in the claims. What is provided is merely an idea for an invention and clearly, further research was necessary in order to identify how it would actually be used.

Due to the large quantity of experimentation necessary to determine what PSGL-1 fragments have specific inhibitory activity for P-selectin/PSGL-1 binding, and can be used as an anti-inflammatory agent in a disparate listing of many diseases, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the

art establishing that cells can use an alternative mechanism for leukocyte rolling during inflammation in the absence of optimal P-selectin/PSGL-1 interaction, and the breadth of the claim which encompass all those diseases with many causes, striking many tissues, and with many different outcomes, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 58-77 are further rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to: a method of reducing inflammation in a subject, comprising administering a composition comprising a fusion protein comprising the amino acids 42-60 of SEQ ID NO: 2 and a non-P selectin ligand amino acid sequence, or comprising administering a composition comprising a soluble P-selectin ligand protein comprising the amino acids 42-88 of SEQ ID NO: 2. What applicant has described in the specification are several P-selectin glycoprotein ligand-1 (PSGL-1) fragments and their Fc chimeric fusion proteins, such as 254.Fc (amino acids 42-295 of SEQ ID NO: 2), 148.Fc (amino acids 42-189), 47.Fc (amino acids 42-88), and 19.Fc (amino acids 42-60), that are capable of binding to P-selectin, and may be able to compete the binding of P-selectin to its natural ligand PSGL-1. Applicant, however, has not described the genus of the fragments comprising the amino acids 42-60, or comprising the amino acids 42-88 of SEQ ID NO: 2, wherein the fragments having P-

selectin ligand activity. There is no teaching regarding the relationship of structure to function, such as how long these molecules are, what structure features are required for the P-selectin ligand activity. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the conjugation products that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until

reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a composition comprising a PSGL-1 fragment of amino acids 42-295, amino acids 42-189, amino acids 42-88, or amino acids 42-60 of SEQ ID NO: 2, but not the full scope of the claimed composition, is adequately described in the disclosure.

Claim Objections

Claim 69 is objected to because of the following informalities:

There is a typographical error in "amino acid 4_2". Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 25, 2006

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